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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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BOZICEVIC, FIELD & FRANCIS LLP 1900 UNIVERSITY AVENUE SUITE 200 EAST PALO ALTO, CA 94303			MONTANARI, DAVID A	
		ART UNIT	PAPER NUMBER	
		1632		

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/809,777	MUCKE ET AL.
Examiner	Art Unit	
David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on _____.
2a) This action is **FINAL**. 2b) This action is non-final.
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-15 is/are pending in the application.
4a) Of the above claim(s) 15 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-14 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 24 March 2004 is/are: a) accepted or b) objected to by the Examiner.

 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 9/16/04.
4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. .
5) Notice of Informal Patent Application (PTO-152)
6) Other: .

DETAILED ACTION

Election/Restrictions

1. During a telephone conversation with Paula A. Borden on August 2nd, 2005 a provisional election was made without traverse to prosecute the invention of Groups I, claims 1-14. Affirmation of this election must be made by applicant in replying to this Office action. Claim 15 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-14, drawn to a method for detecting an amyloid peptide-related neurological disorder in a non-human animal comprising detecting a level of a calcium-responsive gene product in brain tissue of the animal model, classified in class 514, subclass 3.
- II. Claim 15, drawn to a method of detecting an amyloid peptide-related neurological disorder in a living subject comprising administering to the subject a detectably labeled agent that binds a calcium-responsive gene product, classified in class 514, subclass 3.

Groups I and II are distinct. Group I is drawn to a method of drug screening using a transgenic animal. Group II is drawn to a method of drug screening which is also a method of therapy. The method of drug screening using said animals would require materially different and separate protocols from the method of screening and treatment of Group II. For example, Group II will require administration of a

labeling agent to the animal whereas such a step is not required for Group I invention.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

2. Claims 1-14 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting an amyloid peptide-related impairment of spatial learning comprising detecting a level of a calbindin mRNA or polypeptide, a neuuropeptide Y mRNA or polypeptide, or an α -actinin II mRNA or polypeptide in the hippocampus of a transgenic mouse whose genome comprises a transgene encoding a mutant amyloid precursor protein (APP) wherein detection of said mRNA or polypeptides in said transgenic mouse differs from the levels of said mRNA or polypeptides in the hippocampus of a normal control mouse and a method for identifying a candidate agent for treating an amyloid peptide-related impairment of spatial learning comprising administering a test agent to a transgenic mouse whose genome comprises a transgene encoding a mutant APP and detecting a level of a

calbindin mRNA or polypeptide, a neuuropeptide Y mRNA or polypeptide, or an α -actinin II mRNA or polypeptide *in vitro* in hippocampal tissue of said mouse and comparing said mRNA or polypeptide levels in hippocampal tissue to said transgenic mouse not administered said test agent, does not reasonably provide enablement for a method of detecting an amyloid peptide-related neurological disorder comprising detecting a level of any calcium-responsive gene product in the brain of any non-human animal model wherein detection of a level of any calcium-responsive gene product differs from the levels of any calcium-responsive gene product of a normal control mouse and for a method of identifying a candidate agent for treating an amyloid peptide-related neurological disorder comprising administering a test agent to any non-human animal model of an amyloid peptide-related neurological disorder and detecting the level of any calcium-responsive gene product *in vitro* in the brain tissue of said non-human animal and comparing the levels of said gene products to said non-human animal not administered said test agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-14 are drawn to a method for detecting an amyloid peptide-related neurological disorder in a non-human animal model, the method comprising: detecting a level of a calcium-responsive gene product in brain tissue of the animal model; wherein detection of a level of calcium-responsive gene product in the brain tissue that differs from a level of the calcium-responsive gene product associated with a normal control animal is indicative of an amyloid peptide-related neurological disorder in the animal, wherein the non-human animal model is an hAPP_{FAD}/A β transgenic non-human animal model of Alzheimer's Disease, wherein the brain

tissue is a hippocampal brain sample, wherein the brain tissue is a granule cell of the dentate gyrus, wherein the calcium-responsive gene product is selected from a calbindin polypeptide or mRNA, a neuropeptide Y polypeptide or mRNA, an α -actinin II polypeptide or mRNA, and a phospho-ERK polypeptide or mRNA, wherein the neurological disorder is impaired spatial learning, a method for identifying a candidate agent for treating an amyloid peptide-related neurological disorder, the method comprising: administering a test agent to a non-human animal model of an amyloid peptide-related neurological disorder; and detecting a level of a calcium-responsive gene product *in vitro* in brain tissue of the animal; wherein detection of a level of the calcium-responsive gene product in the brain tissue that differs significantly from a level of the calcium-responsive gene product in the absence of the agent indicates that the test agent is a candidate agent for treating an amyloid peptide-related neurological disorder, wherein the non-human animal model is an hAPP_{FAD}/A β transgenic non-human animal model of Alzheimer's disease, wherein the brain tissue is a hippocampal brain sample, wherein the brain tissue is a granule cell of the dentate gyrus, wherein the neurological disorder is impaired spatial learning, wherein the calcium-responsive gene product is selected from a calbindin polypeptide or mRNA, a neuropeptide Y polypeptide or mRNA, an α -actinin II polypeptide or mRNA, and a phospho-ERK polypeptide or mRNA.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the

claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompass detecting an amyloid peptide-related neurological disorder in any non-human animal model, including healthy controls, by detecting the level of any calcium-responsive gene product in any part of the brain of said animal and comparing the level of said calcium-responsive gene product to the level of the calcium-responsive gene product in a normal control, and a method of identifying a candidate agent for treating an amyloid peptide-related neurological disorder comprising administering a test agent to any non-human animal model of an amyloid peptide-related neurological disorder and comparing the level of a calcium-responsive gene product to the level of the calcium-responsive gene product in the absence of said test agent.

Whereas the nature of the invention is a method of detecting a neurological disorder in a non-human animal model, and further using said animal model for drug screening, the art teaches that the field of creating non-human animal models is unpredictable. The claimed methods involve using non-human animal models, with claims 1, and 3-7 using any non-human animal

model, including normal healthy control animals, and claims 8, and 10-14 using any non-human animal model of an amyloid peptide-related neurological disorder. Claims 2 and 9 are directed to any transgenic hAPP_{FAD}/A β non-human animal model of Alzheimer's disease. However, the art at the time of filing teaches that only the creation and use of transgenic mice results in predictable animal models and yet still requires further refinement. Further, even with regard to transgenesis of mice, the art teaches that significant unpredictability still remains, and that attempting transgenesis in any non-human animal would be highly unpredictable for the skilled artisan. The following art summarizes the current issues and unpredictability surrounding transgenesis. Transgenic mouse lines are generated by microinjection of the linear DNA of interest into the nucleus of an oocyte or transfected into embryonic stem (ES) cells, which then randomly integrates into the genome (Ristevski, Molecular Biotechnology, Vol. 29, 2005, pg. 159 col. 1 parag. 2 lines 1-5). Currently only mouse ES cells have been established that result in a transgenic animal (Smith, 2002, J. of Biotechnology, Vol. 99, pg. 3 col. 1, parag. 4 lines 1-3). With regard to transgene integration the art teaches that the site of integration is uncontrolled and yet is critical due to the possibility of integration into a silent locus. Random integration may occur, resulting in the insertional inactivation (insertional mutagenesis) of a gene at the site of integration, resulting in a loss of function that may be mistakenly attributed to over expression of the transgene (Ristevski, pg. 159 col. 1 parag. 2 lines 5-14). Further, insertional mutagenesis of a gene may not be immediately apparent if a recessive gene has been inactivated, as phenotypic abnormalities will not be evident until homozygous transgenic lines have been established (Ristevski, pg. 159 col. 1 parag. 2 lines 14-19). The site of integration may also result in altered tissue specificity, although the promoter used behaves differently at its normal chromosomal

localization, with neighboring regulatory elements potentially influencing the transcriptional activity of the transgene (Ristevski, pg. 159 col. 1 parag. 3 lines 1-7). This is known as chromosomal position effects, where host sequences surrounding the site of transgene integration can alter the expected expression pattern, turning it ectopic or not detectable (Montoliu, 2002, Cloning and Stem Cells, Vol. 4, pg 39, col. 1). With regard to copy number the art teaches that controlling the transgene copy number (usually integration is a singular event with multiple copies integrated in tandem) is also problematic in the generation of transgenic animals (Ristevski, pg. 159 col. 1 parag. 3 lines 7-11). A high tandem copy number results in a gene silencing effect, and further, is undesirable if the effect of a gene dosage is being addressed, as multiple copies will not recapitulate relevant levels of expression (Ristevski, pg. 159 col. 1 parag. 3 lines 11-14 bridge col. 2 parag. 1). With regard to transgene expression, the art teaches bluntly that, "many transgenes work poorly" (Houdebine, 2002, J. of Biotechnology, Vol. 98, pg. 150, col. 1 parag. 4 line 1). Transgene expression is often very low or not specific of the promoter added in the gene construct, and are generally attributed to position effects in chromatin as discussed above (Houdebine, pg. 150, col. 1 parag. 4 lines 1-5). The art continues to teach that a transgene is generally poorly expressed when it contains a cDNA rather than the corresponding genomic DNA sequence with its introns, has multiple copies integrated in the same site, and when a bacterial gene is used (Houdebine, pg. 150 col. 2 lines 4-9). Overexpression of a transgene of interest also has inherent problems. This is often the case when the overproduced protein shares only a part of the properties of an endogenous protein, which can result in inhibition of the endogenous protein, by the transgene of interest working in a transdominant negative manner (Houdebine, pg. 152, col. 2 parag. 4). The art continues that the

generation of transgenic animals routinely involves one of two methods of exogenous DNA delivery to the recipient cells, retroviral infection or microinjection (Smith, pgs. 5-11). However, each method possesses significant unpredictability for the skilled artisan to implement. Retroviral vectors result in inconsistency and irreproducibility of transgene expression due to random integration with host DNA (Smith, pg. 6, col. 1 parag. 2), and instability due to the integrated retroviral DNA possessing the ability to spontaneously reactivate (Smith, pg. 6, col. 1 parag. 5). Microinjection of recipient cells with exogenous DNA presents the problem of mosaicism to the skilled artisan. The majority (\approx 85%) of pronuclear microinjection-derived transgenic founders are mosaics of transgenic and non-transgenic cells (Smith, pg. 7, col. 2 parag. 2 lines 1-4). This becomes problematic since transmission of the transgene is dependent upon the existence and extent of germline colonization by transgene-containing cells, so that when transmission does occur, the transgene is inherited in a mendelian fashion resulting in only a small portion of the transgene being passed onto offspring (Smith, pg. 7, col. 2 parag. 3, bridge pg. 8 col. 1 lines 1-8). Significant restraints also exist for the skilled artisan attempting microinjection of other animal species other than mouse. Cow, pig, and sheep eggs are optically opaque, unlike mice, which makes microinjection of the targeted pronuclei extremely difficult (Smith, pg. 11 col. 2 parag. 1). In view of the art summarized above, the skilled artisan at the time of filing would surmise that the field of transgenesis is very unpredictable making implementation of the claimed methods extremely difficult, and thus would require an undo amount of experimentation without a predictable degree of success to use the claimed methods.

With regard to detecting any amyloid peptide-related neurological disorder in a non-human animal model comprising detecting the level of any calcium-responsive gene product in

any part of the brain of said animal, the art teaches that such a method would be unpredictable. The art teaches that in transgenic mice comprising hAPP_{FAD}/A β there is a significant reduction in the calcium-binding protein calbindin-D_{28k} (CB) only in the hippocampus, specifically granule cells of the dentate gyrus (Palop et al. 2003, PNAS, Vol. 100, pg. 9574 Fig. 1A). Further, said transgenic mice also had impaired spatial learning but not quid learning compared to wild-type mice (Palop, pg. 9573 col. 2 parag. 4). The art continues to teach that the calcium-dependent immediate early gene product c-Fos was also decreased in granule cells of the dentate gyrus in said transgenic mice (pg. 9573 col. 2 parag. 2). The art continues that the exact mechanism by which A β assemblies may reduce CB and c-Fos levels in granule cells remain to be determined, though they might involve alterations in the function of calcium channels and other membrane proteins, chronic inflammation, and formation of pores in cell membranes (pg. 9575 col. 1 parag. 1). Thus the skilled artisan, in view of the arts teaching, would surmise that given the discrepancies between spatial and quid learning in transgenic hAPP_{FAD}/A β mice, that certain calcium-responsive genes are localized only in the hippocampus in said transgenic mice, and that it is still not known how A β affects calcium-responsive genes, the skilled artisan would find the claimed methods unpredictable when practiced in their full breadth.

The working examples provided by the specification teach transgenic hAPP_{FAD}/A β mice, from lines J20 and I5 (Mucke et al., 2000, J. Neuroscience, Vol. 20, pgs. 4050-4058), representing F6-F10 offspring from crosses of heterozygous transgenic with C57BL/6 nontransgenic breeders (pg. 32 parag. 1 lines 1-4), have reduced CB, c-Fos, and α -actinin levels and increased neuropeptide Y levels in the dentate gyrus (pgs. 34-36). The specification continues that the majority of hAPP_{FAD}/A β mice learned to navigate to a visible platform,

demonstrating efficient cued learning, but showed significant deficits in the spatial learning (pg. 40 parag. 3 lines 1-3). The specification continues to teach that only the hippocampus area of the brain was evaluated (pg. 34 parag. 2 bridge pg. 35 lines 1-9). The specification makes no mention of measuring phospho-ERK. The specification continues to teach that a reduction in CB and c-Fos levels correlated with the relative abundance of A β 1-42 but not with hAPP_{FAD} levels, however the exact mechanism by which A β assemblies may reduce CB and c-Fos levels remains to be determined (pg. 39 parag. 3 lines 7-9).

However, the specification had failed to disclose any animal model other than transgenic hAPP_{FAD}/A β mice to be used in the claimed method. Further the specification has failed to teach how any calcium-responsive gene product is related to a neurological disorder. The specification has merely noticed a correlation of certain calcium-responsive genes that increase or decrease in level with the progressive onset of Alzheimer's disease morphology due to the hAPP_{FAD}/A β expression. The specification does not teach or suggest how the claimed calcium-responsive genes increase or decrease in level with hAPP_{FAD}/A β expression, and further does not adequately describe a representative number of calcium-responsive genes that would be affected by hAPP_{FAD}/A β expression. The specification has only measured two learning types, cued and spatial, however this is not representative of all amyloid peptide-related neurological disorders. Further the data for cued and spatial learning is in disagreement, and thus not all amyloid peptide-related neurological disorders can be detected using the claimed methods since wild-type and experimental animals were not significantly different in cued learning tests.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the claimed invention is not enabled for its

full breadth and limiting the scope of the claimed invention to a method of detecting an amyloid peptide-related impairment of spatial learning comprising detecting a level of a calbindin mRNA or polypeptide, a neuopeptide Y mRNA or polypeptide, or an α -actinin II mRNA or polypeptide in the hippocampus of a transgenic mouse whose genome comprises a transgene encoding a mutant amyloid precursor protein (APP) wherein detection of said mRNA or polypeptides in said transgenic mouse differs from the levels of said mRNA or polypeptides in the hippocampus of a normal control mouse and a method for identifying a candidate agent for treating an amyloid peptide-related impairment of spatial learning comprising administering a test agent to a transgenic mouse whose genome comprises a transgene encoding a mutant APP and detecting a level of a calbindin mRNA or polypeptide, a neuopeptide Y mRNA or polypeptide, or an α -actinin II mRNA or polypeptide *in vitro* in hippocampal tissue of said mouse and comparing said mRNA or polypeptide levels in hippocampal tissue to said transgenic mouse not administered said test agent is proper.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1-14 are directed to a method for detecting an amyloid peptide-related neurological disorder in a non-human animal model, the method comprising: detecting a level of a calcium-responsive gene product in brain tissue of the animal model; wherein detection of a level of calcium-responsive gene product in the brain tissue that differs from a level of the calcium-

responsive gene product associated with a normal control animal is indicative of an amyloid peptide-related neurological disorder in the animal..

When the claims are analyzed in light of the specification, the instant invention encompasses detecting the level of any calcium-responsive gene product in brain tissue that is related to an amyloid-peptide-related neurological disorder. However, the specification teaches only the gene products of CB, c-Fos, neuropeptide Y, and α -actinin II are affected in level in response to expression amyloid peptide. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only four genes have been disclosed. The specification does not provide any disclosure as to what the common feature among these four genes or any calcium-responsive genes that would lead to an increase or decrease in their levels due to expression amyloid peptide-related neurological disorder. The specification states that it is not known how an amyloid peptide-related neurological disorder affects a calcium-responsive gene product. The art teaches only that CB and c-Fos levels are affected by an amyloid-peptide related neurological disorder (Palop et al. 2003, PNAS, Vol. 100, pgs. 9572-9577). Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only characteristic described is that genes be calcium-responsive. However, this cannot be used as an identifying characteristics since all species of the claimed genus will have this characteristic. The specification does not teach any other identifying characteristic.

Applicants' attention is directed to the decision in *In re Shokal*, 113, USPQ 283 (CCPA 1957) wherein is stated:

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It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim, *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97, F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such a number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as halogens, consisting of four species, a reduction in practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that applicant is in possession of all calcium-responsive gene products in brain tissue related to an amyloid peptide-related neurological disorder. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-8, and 10-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Vezzani et al. (March 12th 2002, Neuroscience, Vol. 110, pgs. 237-243).

Claims 1, 3-8, and 10-14 are drawn to a method for detecting an amyloid peptide-related neurological disorder in a non-human animal model, the method comprising: detecting a level of a calcium-responsive gene product in brain tissue of the animal model; wherein detection of a level of calcium-responsive gene product in the brain tissue that differs from a level of the

calcium-responsive gene product associated with a normal control animal is indicative of an amyloid peptide-related neurological disorder in the animal, wherein the brain tissue is a hippocampal brain sample, wherein the brain tissue is a granule cell of the dentate gyrus, wherein the calcium-responsive gene product is selected from a calbindin polypeptide or mRNA, a neuropeptide Y polypeptide or mRNA, an α -actinin II polypeptide or mRNA, and a phospho-ERK polypeptide or mRNA, wherein the neurological disorder is impaired spatial learning, a method for identifying a candidate agent for treating an amyloid peptide-related neurological disorder, the method comprising: administering a test agent to a non-human animal model of an amyloid peptide-related neurological disorder; and detecting a level of a calcium-responsive gene product *in vitro* in brain tissue of the animal; wherein detection of a level of calcium-responsive gene product in the brain tissue that differs significantly from a level of the calcium-responsive gene product in the absence of the agent indicates that the test agent is a candidate agent for treating an amyloid peptide-related neurological disorder, wherein the brain tissue is a hippocampal brain sample, wherein the brain tissue is a granule cell of the dentate gyrus, wherein the neurological disorder is impaired spatial learning, and wherein the calcium-responsive gene product is selected from a calbindin polypeptide or mRNA, a neuropeptide Y polypeptide or mRNA, an α -actinin II polypeptide or mRNA, and a phospho-ERK polypeptide or mRNA.

Vezzani et al. teach that neuropeptide Y (NPY) is a 36-amino acid peptide widely distributed in various forebrain areas. Vezzani continues to teach transgenic (tg) rats comprising overexpression of the rat NPY gene have an impaired spatial learning phenotype (pg. 238 col. 1 parag. 2 lines 1-3). Vezzani continues to teach that the anteriorposterior area of the hippocampus

was assayed for NPY mRNA levels (pg. 238 col. 2 last two lines bridge pgs. 239 col. 1 parag. 1).

Vezzani continues that NPY mRNA levels were significantly increased in CA1 pyramidal neurons of tg rats compared to wild-type rats (pg. 240 col. 2 parag. 2-3). Vezzani continues that increased NPY mRNA levels in granule neurons occurred after kainic acid (KA) treatment in wild-type and tg rats (pg. 240 col. 2 parag. 4). Following increased NPY mRNA expression, a 47% increase in NPY levels in the CA1-CA2 micropunches occurs (pg. 242 col. 1 parag. 1 lines 5-10). Tg and wild-type rats were treated with either saline or KA and NYP mRNA levels were evaluated in the CA1 area from horizontal sections of the ventral hippocampus (pg. 241, Fig. 2). Thus Vezzani et al. clearly anticipate the invention of claims 1, 3-8, and 10-14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamb et al. (1997, Human Molecular Genetics, Vol. 6, pgs. 1535-1541) in view of Vezzani et al. (March 12th 2002, Neuroscience, Vol. 110, pgs. 237-243).

Claims 2, and 9 are drawn to a method of detecting an amyloid peptide-related neurological disorder and a method of identifying a candidate agent for treating an amyloid peptide-related neurological disorder in a transgenic non-human animal model of Alzheimer's disease comprising hAPP_{FAD}/A β .

Lamb et al. teach that Alzheimer's disease has several genetic etiologies including mutations in the beta-amyloid precursor protein gene (APP) and mutations in the presenilin 1 gene on chromosome 14 and the presenilin 2 gene on chromosome 1 in autosomal dominant early onset familial Alzheimer's disease (FAD) (pg. 1535, col. 2 lines 1-7). Lamb continues to teach that by generating transgenic mice comprising the entire ~400 kb human APP gene harboring the FAD mutations the proper spatial and temporal expression of mutant APP with appropriate splice donor and acceptor sites needed to generate the entire spectrum of alternatively spliced APP transcripts and encoded proteins occurs resulting in a pathology most similar to early onset Alzheimer's disease (pg. 1536 col. 1 parag. 1). Lamb continues that said tg mice should prove valuable for detailed analysis of the in vivo effects of the APP FAD mutations in a variety of tissues and for testing therapeutic agents that specifically alter APP metabolism and A β production (pg. 1535, Abstract, last sentence). Lamb does not teach a method of detecting an amyloid peptide-related neurological disorder and a method of identifying a candidate agent for treating an amyloid peptide-related neurological disorder in a transgenic non-human animal model of Alzheimer's disease comprising hAPP_{FAD}/A β .

Vezzani et al. teach that neuropeptide Y (NPY) is a 36-amino acid peptide widely distributed in various forebrain areas. Vezzani continues to teach transgenic (tg) rats comprising overexpression of the rat NPY gene have an impaired spatial learning phenotype (pg. 238 col. 1 parag. 2 lines 1-3). Vezzani continues to teach that the anteriorposterior area of the hippocampus was assayed for NPY mRNA levels (pg. 238 col. 2 last two lines bridge pgs. 239 col. 1 parag. 1). Vezzani continues that NPY mRNA levels were significantly increased in CA1 pyramidal neurons of tg rats compared to wild-type rats (pg. 240 col. 2 parag. 2-3). Vezzani continues that

increased NPY mRNA levels in granule neurons occurred after kainic acid (KA) treatment in wild-type and tg rats (pg. 240 col. 2 parag. 4). Following increased NPY mRNA expression, a 47% increase in NPY levels in the CA1-CA2 micropunches occurs (pg. 242 col. 1 parag. 1 lines 5-10). Tg and wild-type rats were treated with either saline or KA and NYP mRNA levels were evaluated in the CA1 area from horizontal sections of the ventral hippocampus (pg. 241, Fig. 2). Vezzani does not teach or suggest using a transgenic non-human animal model of Alzheimer's disease comprising hAPP_{FAD}/A β .

Thus, it would have been obvious to the ordinary artisan at the time of filing to modify the methods of Lamb and Vezzani to detect an amyloid peptide-related neurological disorder and identifying a candidate agent for treating an amyloid peptide-related neurological disorder in a transgenic non-human animal model of Alzheimer's disease comprising hAPP_{FAD}/A β given the motivation provided by Lamb teaching the significance of using tg mice comprising hAPP_{FAD}/A β to screen for therapeutic agents in view of the motivation provided by Vezzani teaching that NPY tg rats have an impaired spatial learning phenotype do to an increase in NPY mRNA and peptide levels.

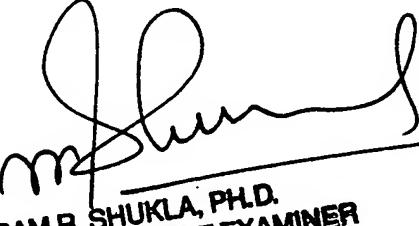
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 1-571-273-8300.

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